CRYSTALLINE FORMS OF A BRUTON'S TYROSINE KINASE INHIBITOR

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 61/655,381 entitled "CRYSTALLINE FORMS OF A BRUTON'S TYROSINE KINASE INHIBITOR" filed on Jun. 4, 2012, which is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

Described herein is the Bruton's tyrosine kinase (Btk) inhibitor 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, including crystalline forms, solvates and pharmaceutically acceptable salts thereof, as well as pharmaceutical compositions that include the Btk inhibitor and methods of using the Btk inhibitor in the treatment of diseases or conditions that would benefit from inhibition of Btk activity.

BACKGROUND OF THE INVENTION

Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

Btk is a key regulator of B-cell development, activation, signaling, and survival. In addition, Btk plays a role in a number of other hematopoetic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor-mediated TNF-α production in macrophages, IgE receptor (FcepsilonRI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation.

1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is also known by its IUPAC name as 1-{(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one or 2-Propen-1-one, 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl-, and has been given the USAN name, ibrutinib. The various names given for ibrutinib are used interchangeably herein.

SUMMARY OF THE INVENTION

Described herein is the Btk inhibitor 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, including pharmaceutically acceptable solvates (including hydrates), polymorphs, and amorphous phases, and methods of uses thereof. Also described are pharmaceutically acceptable salts of the Btk inhibitor, including pharmaceutically acceptable solvates (including hydrates), polymorphs, and amorphous phases, and methods of uses thereof. 1-((R)-3-(4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, as well as the pharmaceutically acceptable salts thereof, are used in the manufacture of medicaments for the treatment of diseases or conditions that are associated with Btk activity. 1-((R)-3-(4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is an irreversible Btk inhibitor.

Also described herein are methods for preparing crystalline forms of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. Further described are pharmaceutical compositions that include the crystalline forms and methods of using the Btk inhibitor in the treatment of diseases or conditions (including diseases or conditions wherein irreversible inhibition of Btk provides therapeutic benefit to a mammal having the disease or condition).

In one embodiment is anhydrous 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

In another embodiment is crystalline anhydrous 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

In a further embodiment is amorphous anhydrous 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

In one aspect is a solvate of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

In one embodiment is a solvate, wherein 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is solvated with methyl isobutyl ketone (MIBK), toluene or methanol. In one embodiment is a solvate, wherein 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is solvated with methyl isobutyl ketone (MIBK) or toluene. In one embodiment is a solvate, wherein 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is solvated with methanol.

In a further embodiment, the solvate is anhydrous.

In another embodiment the solvate is crystalline.

In yet another embodiment the solvate is amorphous.

In one aspect, described herein is a crystalline Form A of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one that has at least one of the following properties:

(a) an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in FIG. **1**;

(b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 5.7±0.1° 2-Theta, 13.6±0.1° 2-Theta, 16.1±0.1° 2-Theta, 18.9±0.1° 2-Theta, 21.3±0.1° 2-Theta, and 21.6±0.1° 2-Theta;

(c) substantially the same X-ray powder diffraction (XRPD) pattern post storage at 40° C. and 75% RH for at least a week;

(d) substantially the same X-ray powder diffraction (XRPD) pattern post storage at 25° C. and 97% RH for at least a week;

(e) Infrared (IR) spectrum substantially similar to the one set forth in FIG. **2**;

(f) Infrared (IR) spectrum weak peaks at about 1584 cm^{-1}, about 1240 cm^{-1}, about 1147 cm^{-1}, about 1134 cm^{-1}, about 1099 cm^{-1}, and about 1067 cm^{-1};

(g) a DSC thermogram substantially similar to the one set forth in FIG. **3**;

(h) a thermo-gravimetric analysis (TGA) thermogram substantially similar to the one set forth in FIG. **4**;

(i) a DSC thermogram with an endotherm having an onset at about 154° C. and a peak at about 157° C. and an exotherm at about 159° C.;

(j) non-hygroscopicity;

(k) an observed aqueous solubility of about 0.013 mg/mL at about pH 8;